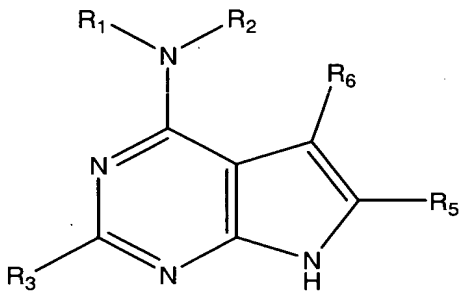
In The Specification

Please replace the structure appearing on page 10, lines 5-15 with the following structure:

C1



Please the paragraphs on page 11, lines 14-17 with the following paragraphs:

C2

wherein R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

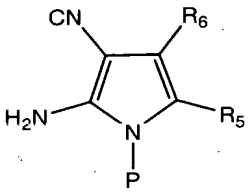
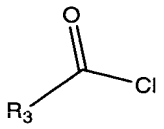
wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl.

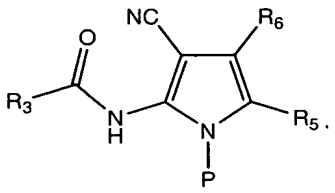
Please replace the paragraph on page 15, lines 26-29 with the following paragraph:

C3

This invention also provides a combination therapy for glaucoma, comprising a compound of structure IV, V or VI, and a prostaglandin agonist, β2 agonist, or a muniscrinic antagonist.

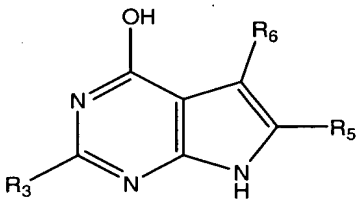
Please replace the structures and text appearing on page 55, lines 8-38 with the following:

a) reacting  and 

to provide 

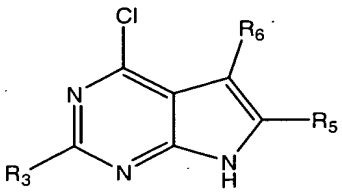
wherein P is a removable protecting group;

b) treating the product of step a) under cyclization conditions to provide

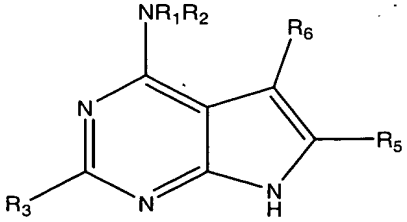


;

c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with NHR_1R_2 to provide



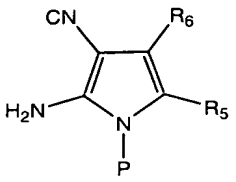
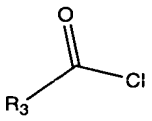
Please replace the paragraphs on page 56, lines 21-24 with the following paragraphs:

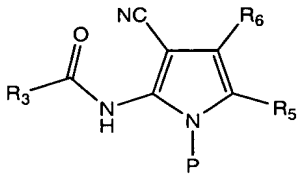
C5

wherein R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl.

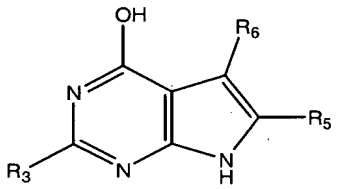
Please replace the structure and text appearing on page 57, lines 1-38 with the following:

a) reacting  and 

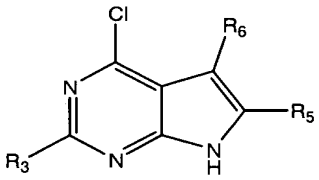
to provide 

wherein P is a removable protecting group;

b) treating the product of step a) under cyclization conditions to provide

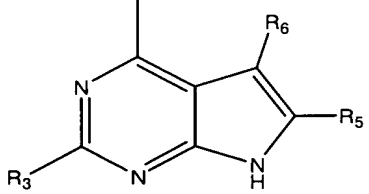
 ;

c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with $NH_2CH_2(CH_2)_mCH_2NHC(=O)R_1$ to provide

$NH_2CH_2(CH_2)_mCH_2NHC(=O)R_1$



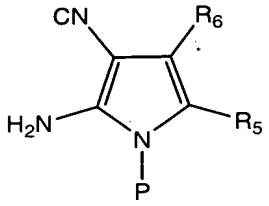
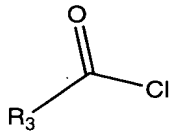
Please replace the paragraphs appearing on page 58, lines 7-16 with the following paragraphs:

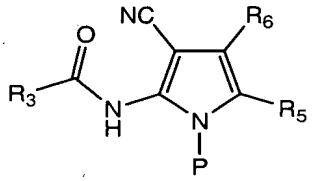
wherein R_3 is aryl, substituted aryl, heteroaryl;

wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl

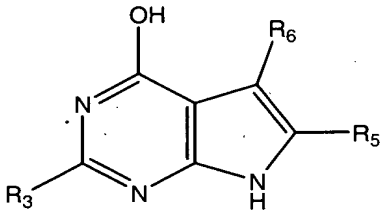
Please replace the structures and text appearing on page 59, lines 1-38 with the following:

a) reacting  and 

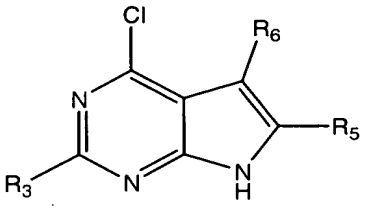
to provide 

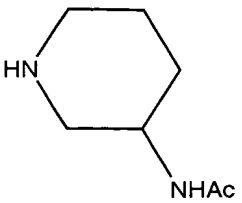
wherein P is a removable protecting group;

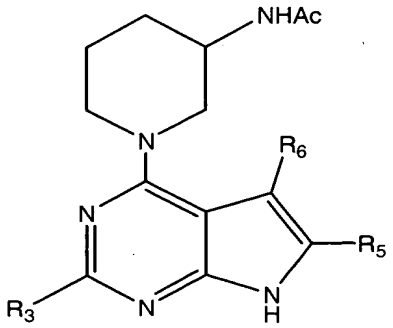
b) treating the product of step a) under cyclization conditions to provide

 ;

c) treating the product of step b) under suitable conditions to provide

 ; and

d) treating the chlorinated product of step c) with 

to provide 

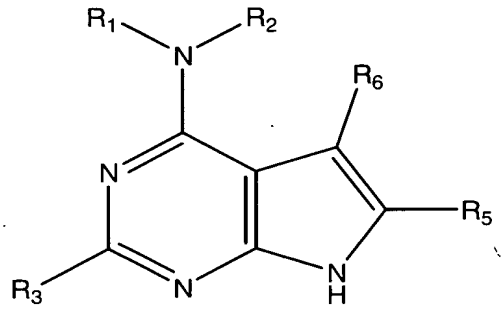
Please replace the paragraphs appearing on page 60, lines 1-10 with the following paragraphs:

wherein R_3 is unsubstituted aryl;

wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and the nitrogen together form a ring system of between 4 and 7 members; and

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl

Please replace the structure appearing on page 60, lines 15-21 with the following structure:



Please replace the period appearing at the end of page 61, line 1, with a semicolon.

Please the paragraphs appearing on page 61, lines 21-24 with the following paragraphs:

wherein R_5 is H, alkyl, substituted alkyl, aryl, or substituted aryl; and

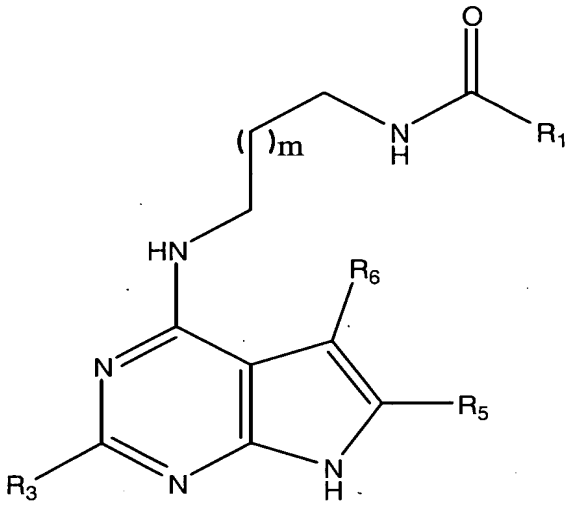
wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl.

Please replace the paragraphs appearing on page 62, lines 3-8 with the following paragraphs:

In another embodiment of the compound, R_6 is hydrogen or methyl.

In another embodiment of the compound, R_5 is hydrogen, methyl, phenyl, 3-chlorophenyloxy methyl, or *trans*-2-phenylamino methyl pyrrolidino methyl.

Please replace the structure appearing on page 62, lines 12-23 with the following structure:



Please replace the paragraphs appearing on page 62, line 31 to page 63, line 8 with the following paragraphs:

wherein R_3 is aryl, substituted aryl, or heteroaryl;

wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and

the nitrogen together form a ring system of between 4 and 7 members; and

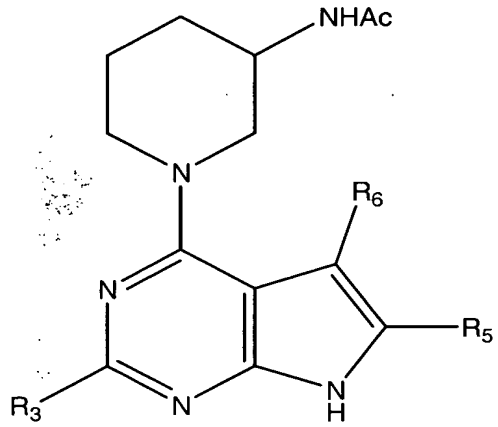
wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl.

In one embodiment of compound V, m is 0 and R_3 is phenyl.

In another embodiment of compound V, m is 1 and R_3 is phenyl.

In another embodiment of compound V, m is 2 and R_3 is phenyl.

Please replace the structure appearing on page 67, lines 2-10 with the following structure:



Please replace the paragraphs appearing on page 67, lines 14-23 with the following paragraphs:

wherein R_3 is unsubstituted aryl.

wherein R_5 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $-C(R_9)(R_{10})NR_7R_8$, wherein R_9 and R_{10} are each H or alkyl, wherein R_7 and R_8 are each alkyl or cycloalkyl, or R_7, R_8 and

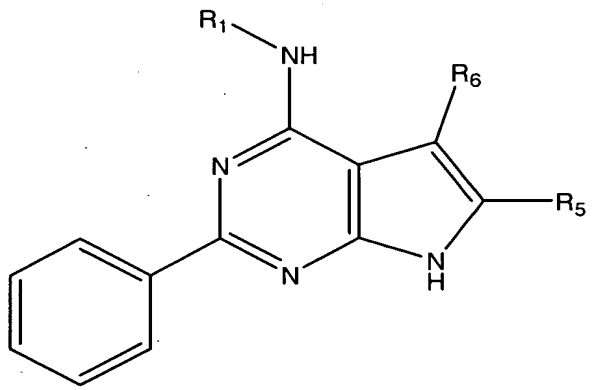
C16 concl'd

the nitrogen together form a ring system of between 4 and 7 members; and

wherein R_6 is H, alkyl, substituted alkyl, or cycloalkyl.

Please replace the structure appearing on page 69, lines 2-10 with the following structure:

C17



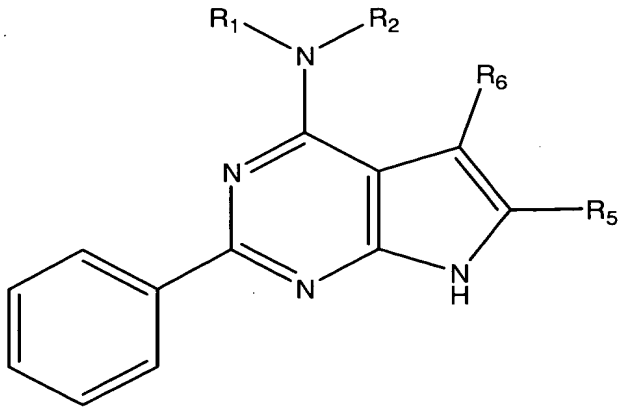
Please replace the paragraph appearing on page 69, lines 23-24 with the following paragraph:

C18

wherein R_5 and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

Please replace the structure appearing on page 80, lines 2-12 with the following structure:

C19



Please replace the paragraph appearing on page 80, lines 21-22 with the following paragraph:

C20

wherein R_5 and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.

Please replace the paragraph appearing on page 147, lines 15-19 with the following paragraph:

C21

Compound 1712 (Table 15 below): ^{1}H-NMR (200MHz, CD_3OD) d 3.02 (m, 2H), 3.92 (m, 2H), 5.09 (2, 2H), 6.53 (s, 1H), 6.90-7.04 (br s, 1H), 6.92 (m, 2H), 7.02 (m, 1H), 7.21 (dd, 1H, J = 8.2Hz), 7.40 (m, 3H), 7.50-7.80 (br s, 1H), 8.33 (m, 2H). MS (ES): 445.1 (M^++1).

The changes to the initially submitted pages are indicated in the marked up pages attached hereto as **Exhibit A**. The changes conform the numbering of the R groups in the application to the numbering scheme found on pages 16, 20 and 93 of the specification as originally filed and correct minor defects. No new matter is introduced.

Please add the following paragraphs after the paragraph ending on page 43, line 30:

N.E. See amdt B

-- **Carrier Linkages for Various Functional Groups**

a. Alcohols and Carboxylic Acids. There are several reasons why the most common prodrug form for drugs containing alcohol or carboxylic acid functional groups is an ester. First, esterases are ubiquitous, so metabolic regeneration of the drug is a facile process. Also, it is possible to prepare ester derivatives with virtually any degree of hydrophilicity or lipophilicity. Finally, a variety of stabilities of esters can be obtained by appropriate manipulation of electronic and steric factors. Therefore, a

multitude of ester prodrugs can be prepared to accomodate a wide variety of problems that require the prodrug approach.

Alcohol-containing drugs can be acylated with aliphatic or aromatic carboxylic acids to decrease water solubility (increase lipophilicity) or with carboxylic acids containing amino or additional carboxylate groups to increase water solubility. Conversion to phosphate or sulfate esters also increases water solubility. By using these approaches a wide range of solubilities can be achieved that will affect the absorption and distribution properties of the drug. These derivatives also can have an important effect on the dosage form, that is, whether used in a tablet form or in aqueous solution. One problem with the use of this prodrug approach is that in some cases the esters are not very good substrates for the endogenous esterases, sulfatases, or phosphatases, and they may not be hydrolized at a rapid enough rate. When that occurs, however, a different ester can be tried. Another approach to accelerate the hydrolysis rate could be to attach electron-withdrawing groups (if a base hydrolysis mechanism is relevant) or electron-donating groups (if an acid hydrolysis mechanism is important) to the carboxylate side of the ester. Succinate esters can be used to accelerate the rate of hydrolysis by intramolecular catalysis. If the ester is too reactive, substituents can be appended that cause steric hindrance to hydrolysis. Alcohol-containing drugs also can be converted to the corresponding acetals or ketals for rapid hydrolysis in the acidic medium of the gastrointestinal tract.

Carboxylic acid-containing drugs also can be esterified; the reactivity of the derivatized drug can be adjusted by the appropriate structural manipulations. If a slower rate of ester hydrolysis is desired, long-chain aliphatic or sterically hindered esters can be used. If hydrolysis is too slow, addition of electron-withdrawing groups on the alcohol part of the ester

can increase the rate. The pKa of a carboxylic acid can be raised by conversion to a choline ester or an amino ester.

b. Amines. N-Acylation of amines to give amide prodrugs is not commonly used, in general, because of the stability of amides toward metabolic hydrolysis. Activated amides, generally of low basicity amines, or amides of amino acids are more susceptible to enzymatic cleavage. Although carbamates in general are too stable, phenyl carbamates (RNHCO2Ph) are rapidly cleaved by plasma enzymes, and, therefore, they can be used as prodrugs.

The pKa values of amines can be lowered by approximately 3 units by conversion to their *N-Mannich bases*. This lowers the basicity of the amine so that at physiological Ph few of the prodrug molecules are protonated, thereby increasing its lipophilicity. For example, the partition coefficient between octanol and phosphate buffer, pH 7.4, for the N-Mannich base derived from benzamide and the decongestant phenylpropanolamine is almot 100 times greater than that for the parent amine. However, the rate of hydrolysis of N-Mannich bases depends on the amide carrier group; salicylamide and succinimide are more susceptible to hydrolysis than is benzamide.

Another approach for lowering the pKa values of amines and, thereby, making them more lipophilic, is to convert them to imines (*Schiff bases*); however, imines often are to labile in aqueous solution. The anticonvulsant agent progabide (8.3) is a prodrug from of γ-aminobutyric acid, an important inhibitory neurotransmitter. The lipophilicity of 8.3 allows the compound to cross the blood-brain barrier; once inside the brain it is hydrolized to γ-aminobutyric acid.

c. Carbonyl Compounds. The most important prodrug forms of